12. (new) A production method of a cirrhosis scid mouse model characterized by comprising the steps of administering an anti-asialo GM 1 antibody into a scid mouse, and transplanting a human cirrhosis tissue affected with cirrhosis in a kidney of the scid mouse.

REMARKS

Claims 1 thru 10 are currently pending in the application. Claims 1, 6, 7, 9 and 10 have been amended. Claims 2, 3, 4, 5 and 8 have been canceled without prejudice. Although Applicants have canceled claims 2, 3, 4, 5 and 8 herein, they respectfully reserve the right to prosecute identical or similar claims in this, or a related application. Claims 11 and 12 have been added. The specific grounds for rejection and Applicant's response to them are set forth in detail below.

1. The information disclosure statement filed 1/14/2005 fails to comply with 37 CFR 1.98(a)(3)(ii).

> The Examiner states that " The information disclosure statement filed 1/14/2005 fails to comply with 37 CFR 1.98(a)(3)(ii), which requires a copy of the translation if a written English-language translation of a non-English-language document, or portion thereof, is within the possession, custody, or control of, or is readily available to any individual designated in § 1.56(c). It has been placed in the application file, but the information referred to therein has not been fully considered, since article is in the Japanese language.

Applicants are in the process of preparing an English translation of this publication which should be available within 2 weeks. Applicants will submit the translated publication under separate cover in a Supplemental Information Disclosure Statement.

2. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The Examiner states that, " Claims 1-10 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a SCID

mouse model of human cirrhosis, characterized in that a human hepatic tissue affected with cirrhosis is transplanted in the kidney of said mouse; does not reasonably provide an enablement for a cirrhosis model in numerous species of animals, wherein the animals are immune deficient nude or SCID animals, and said animal models further comprising transplanting of human xenogeneic hepatic tissue to any organ or tissue of the recipient, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claims 1-10 encompass an animal model of cirrhosis, characterized in that a human hepatic tissue affected with cirrhosis is transplanted in a tissue of an animal having an immune deficiency. As such, the claims embrace numerous species of animals that may serve as an animal model. Additionally the claims envision transplantation into any of the tissues of the recipient animal. Moreover, the claims embrace recipient animals having an immune deficiency that may involve B. T or NK cells.

The instant specification states that the recipient "animal is not particularly limited, but it is possible to use a mouse, a rat, a guinea pig, a hamster, a rabbit, a dog and the like." (fourth paragraph, p. 5). Additionally stating: "The animal tissue in which the hepatic tissue is transplanted is not particularly limited, but it is preferable to use a tissue which maintains a high blood flow." (last paragraph, p. 3). The specification further includes the utility of immune deficient animals whose immune response is partially defective (fourth paragraph, p. 4). Examples of immune-deficiency animals provided include " a nude animal whose T-cell-dependent immune response capability has been made defective" and "a scid

animal whose T-cell and B-cell dependent immune response capability has been made defective" (second paragraph, p. 9).

When given their broadest reasonable interpretation, in view of the as filed specification, the claims embrace a cirrhosis model in numerous species of animals, wherein the animals are immune deficient nude or SCID animals, and said animal models further comprising transplanting of human xenogeneic hepatic tissue to any organ or tissue of the recipient animal.

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the person of skill in the art would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to transplant human hepatic tissue into any of a number of tissues of a xenogeneic recipient animal; to further provide immune deficiency into numerous animals; and to produce any of numerous species of animals to serve as models of human cirrhosis, as claimed in the instant application.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art with regard to animal models of human hepatic xenotransplantation is discussed by Kay et al. (U.S. Patent No: 6,660,905, filed Jul. 12, 2000). The authors state that "Many different approaches for creating an animal model for liver disease using hepatocellular transplantation have been tried over the years... While hepatocellular transplantation within the same or relate species has been established...Previous mouse or rat models show a low rate of persistence of hepatocytes function" (columns 2 and 3, bridging).

Regarding the use of immune deficient animals as transplantation recipients, Habu et al. (U.S. Patent Publication No.: 2004/0016007, filed May 15, 2001) state that "a severe combined immunodeficiency disease (SCID) mouse is used as a host because the mouse does not frequently develop rejection and is incapable of producing mouse antibodies...and is known to be deficient in mature T cells and B cells, the major cells responsible for the immune system." (first and second columns bridging, p. 1).

While both nude mice and rats have been described in the prior art, the prior art is silent on the production of SCID animals, other than mouse. The prior art is further silent on the ability to engraft xenogeneic tissue into any of the multitude of tissues of an animal. Hence, the nature of the invention is not reasonably predictable for any of the numerous animals encompassed by the instant claims or the various recipient tissues, as claimed, due to the unpredictability of the foregoing. Therefore, it would require further and undue experimentation to investigate the various parameters regarding the xenotransplantation of human hepatic tissue.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of numerous animals that may serve as models of human cirrhosis. The specification does not provide any specific guidance to overcome the art recognized unpredictability in introducing human xenogeneic tissue to any of a number of tissues or organ sites in a recipient animal. Moreover, the specification does not provide a description for successful engraftment of a xenogeneic tissue in a nude animal.

The specification does not teach how to make a model animal of human cirrhosis for any other species other than mice, or any other immunodeficient animal, other than SCID mice. The specification further does not teach the xenografting of human hepatic tissue to any recipient site other than kidney.

The specification teaches the use of SCID mice (Example 1, p. 13), and SCID mice having defective NK cell function (Example 2, p. 14), and the transplantation of human hepatic tissue beneath the kidney membrane of said mice. The rate of tissue engraftment was found to be 15% for SCID mice and 35% for SCID mice treated with GM 1 antibodies targeting NK cells (p. 15). The examples did not describe transplantation of xenogeneic tissue to any other recipient site or the use of any other animals as recipients, or the use of nude animals as recipients.

In view of the lack of teachings or guidance provided by the specification with regard to the xenogeneic transplantation of human hepatic tissue to organs other than kidney, or to animals other than SCID mice, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of a cirrhosis model in numerous species of animals, wherein the animals are immune deficient nude of SCID animals, or said animal models further comprising transplanting of xenogeneic tissue to any organ or tissue of the recipient, as claimed in the instant application. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps, especially in light of the evidence that is contrary to the instant claims.

Level Of Skill In The Art

Because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Summary

> Applicant is therefore enabled for a SCID mouse model of human cirrhosis, characterized in that a human hepatic tissue affected with cirrhosis is transplanted in the kidney of said mouse. In the instant case, as discussed above, in a highly unpredictable art where the availability of immune deficient animals is limited to a few rodents, and the xenotransplantation of tissues is limited to certain highly vascularized tissues, and where optimal conditions for transplantation and maintenance of tissues is yet to be achieved, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Applicants have amended the claims to add a limitation that the human cirrhosis tissues are transplanted to a kidney of a scid mouse. Applicants believe the amended claims are enabled and respectfully request reconsideration.

3. Claims 1-5, 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al. (U.S. Patent No. 6,660,905, filed july 12, 2000.

> The Examiner states that, " Claims 1-5, 8, and 10 encompass a scid mouse model of human cirrhosis characterized in that a human hepatic tissue affected with cirrhosis is transplanted in a kidney of mouse.
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> Kay et al. teach mice comprising engrafted functional human hepatocytes or fragments of human hepatic tissue (Title and Abstract). They state that an "object of the invention to provide an animal model for human disorders involving exposure to chemicals or toxins, such as alcoholic cirrhosis." (column 3). Specifically described are human hepatocytes transplanted in the kidney capsule of NOD/SCID mice (column 4, description of Fig. 1). The instant specification states that a scid animal is defective in both B and T cell immune response capability (p. 5, second paragraph), therefore the limitation of claim 4 is embraced by SCID mice.
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> Therefore, each and every element and limitation regarding the human hepatic tissue cirrhosis mouse model of claims 1-5, 8, and 10 is anticipated and effectively addressed by Kay et al., absent evidence to the contrary.

Applicants respectfully disagree. The invention as now claimed in amended claim 1 relates to a scid mouse model in which human cirrhosis tissues have been transplanted in the kidney. It should be noted here that the human cirrhosis tissues are dysfunctional tissues.

As pointed out by the Examiner, Kay et al., (USP No. 6,660,905 (filed July 12, 2000) teaches "mice comprising engrafted functional human hepatocytes or fragments of human

hepatic tissue." This publication merely teaches an animal model for human disorders, using functional tissues.

In other words, Kay et al. does not disclose anything about an animal model for human disorders using dysfunctional tissues.

Thus, the invention set forth in claim 1 is novel over Kay et al. Applicants respectfully request reconsideration.

4. Claims 6, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. as applied to claims 1-5 above, and further in view of Habu et al. (U.S. Patent Publication No.: 2004/0016007, filed May 15, 2001).

> The Examiner states that, " Claims 6 and 7 are drawn to the cirrhosis mouse model of claims 1-5, wherein the NK cell dependent immune response capability of the animal is made defective by administering an anit-asialo GM1 antibody.
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> Kay et al. do not teach an immune deficient animal defective in NK cell immune response capability or the use of the GM1 antibody. Habu et al. describe the use of SCID mice for transferring human hematopoietic stem cells (Abstract). Habu et al. state: "A NOD-SCID mouse was selected as a recipient mouse because it is incapable of producing mouse antibodies and, owing to a reduced activity of NK cells, is less likely to cause rejection." (paragraph [0013], p. 2). Further stating: " For further reducing the activity of NK cells, it is also effective to administer to the mice an antibody specific to NK cells. Examples of antibodies specific to NK cells include anti-asialo GM1 antibody" (paragraph [0036], p. 3).
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> The methods described by Kay et al. and Habu et al. are directed to the transplantation of human cells and tissues into SCID mice. A person of ordinary skill in the art would have been motivated to combine the SCID mouse hepatic cirrhosis model of Kay et al., and the SCID mouse NK deficient transplantation model of Habu et al., to increase the success of engraftment of transplanted xenogeneic hepatic tissue.
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> Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the SCID mouse hepatic cirrhosis model of Kay et al., and the SCID mouse NK deficient transplantation model of Habu et al., to increase the success of engraftment of transplanted xenogeneic hepatic tissue, resulting in the practice of the instantly claimed invention. A person of ordinary skill in the art, would have been motivated to combine the elements of NOD-SCID mouse, and the administration of GM1 antibody to further make defective the immune response capability of NK cells, and would have a reasonable expectation of success in increasing the

> effectiveness of transplantation of human cirrhosis hepatic tissue taught by Kay et al. Moreover, each limitation of claims 6 and 7 is effectively described by the teachings of Kay et al., and Habu et al.
>
> Claim 9 is directed to a model of human cirrhosis characterized in that a human hepatic tissue affected with cirrhosis is transplanted in a tissue of an animal, wherein the transplanted tissue is classified as Child A in terms of severity. The classification of hepatic cirrhosis based on the severity of the disease, was well established in the prior art. Kay et al. teach: "Phenotyping of the xenogeneic hepatocytes to verify their origin and stage of developmental progression may be performed by biopsy of the engrafted hepatocytes followed by standard histological methods" (column 12). Therefore, the invention of Kay et al. is applicable to liver tissue transplantation at any stage of cirrhosis permissible for transplantation. Therefore, it would have been obvious for a person of ordinary skill in the art, at the time of the present invention to use human hepatic tissue having a stage of cirrhosis classified as Child A, in the transplantation model of Kay et al., to increase the success of engrafting, as the Child A staged hepatocytes are low in disease severity and hence have a better prognosis for survival following their transplantation, thus resulting in the animal model of the instant invention. A person of ordinary skill in the art, would have been motivated to utilize the NOD-SCID mouse model as the transplantation recipient for human hepatic tissue classified as Child A to increase the degree of engraftment, and would have a reasonable expectation of success in increasing the effectiveness of transplantation of human cirrhosis hepatic tissue taught by Kay et al.
>
> Hence, the claimed invention a whole is prima facie obvious, absent evidence to the contrary.

Applicants respectfully disagree. As to Habu et al. (U.S.P Publication No.2004/0016007 (filed May 15, 2001), the reference does not disclose or suggest an animal model for human disorders using dysfunctional tissues either.

For the reasons set out above, the invention as set forth in claim 1 cannot be readily attained from Kay et al. and Habu et al. The invention of claim 1 is therefore not obvious from these references.

Claims 10 and 12 also recite the use of dysfunctional tissues. Therefore, for the same reason as for claim 1, claims 10 and 12 are not obvious from Kay et al. and Habu et al.

The foregoing publication, *Virus,* 49(1), 33-39 (1999), describes mice in which functional tissues (pieces of human fetal hepatic tissues, fetal thymus tissues) are engrafted into the kidney

membrane of skid mice. The publication therefore does not disclose or suggest an animal model for human disorders using dysfunctional tissues. Applicants respectfully request reconsideration.

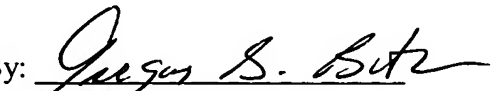
Applicants request the entry of the changes to the claims requested above. No new matter has been added by the amendments to the claims. Applicants submit that the present application and claims, as amended, is in condition for allowance, and, accordingly, early consideration and allowance of the application is respectfully requested.

If for any reason an additional fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

If the undersigned can be of any assistance in advancing the prosecution of this case, the Examiner is invited to contact him through the information given below.

Respectfully submitted,

Date: August 3, 2006

By: 

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